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DO MAMMOGRAPHY'S BENEFITS JUSTIFY ITS HARMS FOR BREAST RANDOMIZED CANCER DETECTION? SYSTEMATIC REVIEW AND META-ANALYSIS OF LONG-TERM CONTROLLED TRIALS

Nura Nasser Alahmadi*[1], Thabat Abdullah Alfraidi[1], Nourah Ahmad Alsumairi[2], Abdulaziz Ali Saeed Al Shamlah[3], Ahmed Yahya Ahmed Mushari[3], Abdullah Ali Alqarni[4] and Moustafa Radwan[5]

[1]Faculty of Medicine, Taibah University, Saudi Arabia.
[2]Faculty of Medicine, Taif University, Saudi Arabia.
[3]Faculty of Medicine, King Khalid University, Saudi Arabia.
[4]Faculty of Medicine, King Saud University, Saudi Arabia.
[5]Department of Radiology, Taibah University, Saudi Arabia.

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***Corresponding Author**
Nura Nasser Alahmadi
Faculty of Medicine, Taibah University, Saudi Arabia.
Nalahmadi93@gmail.com

BACKGROUNDS

Mammography usefulness is questionable in terms of breast cancer over diagnosis and mortality, clinically subtle cancers which would not otherwise be detected. Therefore, we systematically reviewed the published randomized controlled trials (RCTs) about the benefits and harms of mammography for breast cancer detection. **Methods:** We searched SCOPUS, PubMed, Cochrane CENTRAL, and Web of Science for RCTs assessing the harms and benefits of mammography for breast cancer detection. We extracted and analyzed data by RevMan version 5.3 for windows. P value lower than 0.05 was considered statistically significant. **Results:** Eleven eligible RCTs were involved in the final analysis (Subjects n=673573). The overall effect estimates showed that mammography significantly reduced the breast cancer mortality rates, regardless of age group (RR=0·80(95%) CI [0·73–0·89], P <0.001). The absolute risk reduction showed that among 235 women invited to screening, the mammography prevented one cancer death. The overall percentage of the over diagnosis, defined as excess cancers as a rate of cancers diagnosed over long-term follow-up among invited women for screening, was 19% (95% CI [15·2–22·7]). **Conclusion:** Mammography screening may modestly decrease mortality of breast

cancer but with a high rate of over diagnosis occurs. The currently published trials have a lot of limitations and whose relevance to screening programs of present-day could be misbelieve**.**

KEYWORDS: Mammography, Breast Cancer, Diagnostic Accuracy.

INTRODUCTION

Breast cancer is considered the most commonly encountered cancer among women worldwide, and the second most common reason of cancer-related deaths among women, following lung cancer.[1] Moreover, 40,290 deaths of breast cancer were foreseeable to happen in 2015 among United States women.[2] There is a solid body of evidence that linked detection of early-stage cancer cells with a favorable prognosis.[3] Therefore, early detection of breast cancer is an essential component for a significant decreasing in death rates due to breast cancer. Mammography is an X-ray imaging technique for visualization of breast tissue, which is a widely considered as the most useful preliminary screening procedure for early detection of breast cancer, even before cancer could be felt.[4] According to US Preventive Services Task Force, mammography screening is recommended biennial for women aged between 50 and 74 years, while the decision of screening for women aged less than 50 years, or more than 75 years, should be based on personal values and risks.[5]

Despite these recommendations, the clinical utility of regular mammography screening is still controversial. Based on the 2009 U.S. Preventive Services Task Force report, there is a lack of evidence that supports the mammography effectiveness in decreasing the mortality of breast cancer among women age of 40s and 70s.[6] Moreover, a recent Cochrane review revealed that mammography did not significantly decrease mortality of breast cancer; while one death is expected to be prevented for every 2000 invited women.[7] However, lower numbers of invited women for screening per one death prevention were reported in other reviews.[8,9]

The diagnostic accuracy of mammography is another concerns. False positive results may trigger fear and worries in women, with subsequent additional imaging and biopsies.[10] Nelson and colleagues reported a high proportions of false-positive results and recommendations for additional imaging through women aged between 40 and 49 years old, which minimize with age.[11] Even greater false positive results were reported in a subsequent systematic review.[8] An additional drawback of mammography screening is the rate of over

diagnosis, defined as the diagnosis of clinically subtle cancers that would not otherwise be detected.[12]

In order to address the current heterogeneity in the published literature, we conducted this systematic review and meta-analysis on long follow-up trials about the benefits and harms of breast cancer detection using mammography.

MATERIALS AND METHODS

Inclusion and Exclusion criteria

We included randomized controlled trials (RCTs) that fulfilled the following criteria: A) RCTs that invited women, without previously diagnosed, for screening with mammography, B) RCTs which compared the mammography group with control group that did not undergo mammography screening and C) RCTs which reported at least the mortality rate from breast cancer. In the case of multiple reports, we included the most relevant publication which reports the longest duration of follow-up.

We excluded the following studies: 1) non-English studies, 2) studies provide unreliable data for extraction and 3) conference and thesis papers.

Literature Search Strategy: We searched SCOPUS, PubMed, Web of Science, and Cochrane CENTRAL till December 2017 through the following search queries were used ("mammography" AND "breast cancer"). No restrictions were imposed regarding the date of publication, population's age, and the country of origin.

Data Extraction: We extracted the following data, independently: 1) the summary characteristics of the included studies; 2) the baseline characteristics of the included population; 3) the risk of bias domains, and 4) the clinical outcomes of each RCT. Another reviewer resolved disagreements.

Quality assessment: The quality of each of the included studies was assessed according to Cochrane risk of bias tool[13] which included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias. Each domain was judged to be of low, unclear or high risk of bias in all included studies.

Measures of mammography effect: Studies that assessed the effectiveness of mammography reported the following outcomes: mortality rate from breast cancer, the mortality rate from all cancers, and harms of mammography. Over diagnosis was defined as excess cancers as a proportion of cancers diagnosed over long-term follow-up in women invited for screening.

Dealing with missing data: Missing standard deviation (SD) of mean change from baseline was calculated from standard error or 95% confidence interval (CI) according to Altman and Bland (2005).[14]

Data Synthesis: Dichotomous data were collected as relative risk (RR) in a random-effect model by Mantel Haenzel (M-H) method. We used RevMan version 5.3 for windows. We evaluated and interpreted heterogeneity depending on the recommendations in the Cochrane Handbook for Systematic Reviews and Meta-analysis (Chapter 9).

RESULTS

Search results: We retrieved 4647 unique citations. A total of 35 publications were identified after titles and abstracts screening. From which, 11 unique RCTs (nine publications) with a total of 654989 women (Mammography group n=318819 and control group n=336170) were involved in the present systematic review and meta-analysis. (See PRISMA flow diagram; Figure.1).

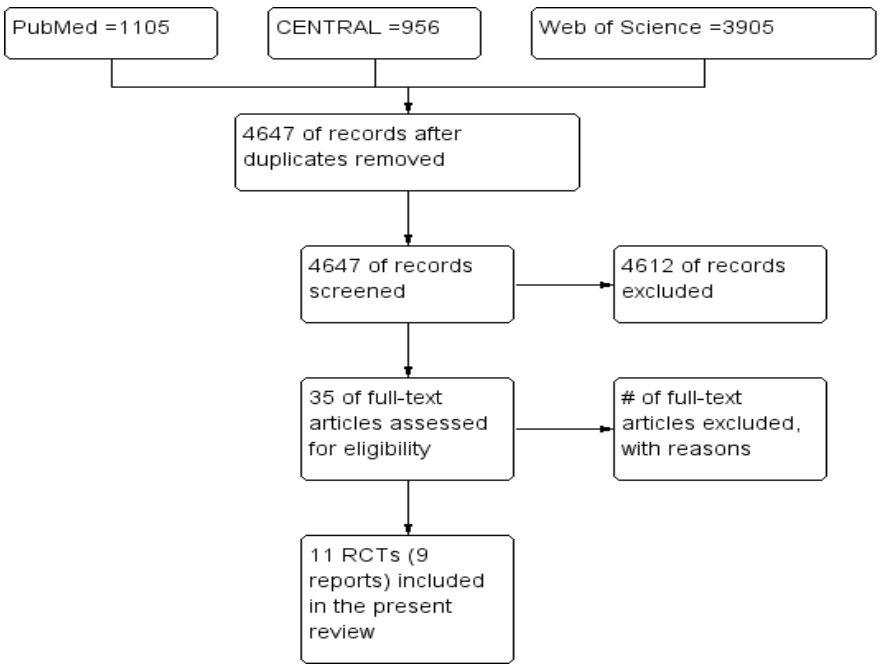

Figure. 1: Prisma flow diagram.

Summary of the characteristics of the included studies

The age range of the women within the included trials ranged between 39 and 74 years old. The Swedish Two-County study was the only trial that included women above 64 years old.[16] The UK Age trial included the largest number of the women (N =160840).[17] The mean mammography screening duration was 6.5 years (SD =2.7 years); while the mammography screening ranged from 12 to 32 months. Only the Canadian study compared the mammography to physical and self-examination.

As mentioned before, we included reports with the longest duration of the follow-up. Nystrom and colleagues reported the results of the 20+ years of follow-up in the randomized controlled mammography trials that's conducted in Sweden.[18] The mean duration of follow-up was 21.9 years (SD =6.7 years); while the duration of follow-up ranged between 14 and 30 years.

Notably, the included studies showed a significant heterogeneity in their conclusions. The overall effect estimates of the four included Swedish RCTs showed the overview revealed a significant 15% relative decreasing in breast cancer mortality because of an invitation to screening using mammography.[18] Similarly, the Swedish Two-County Study revealed a highly significant decreasing in mortality due to breast cancer following mammography screening.[16] Regarding the screening effect before the 50 years of age, The Edinburgh study was the only trial which reported a significant benefit from the introduction of screening to this age group.[19] In contrary, Canada, New York HIP, and UK Age trials reported no significant decreasing in mortality resulting from breast-cancer through this age group.[17,20,21]

Table. 1: Shows the summary of the included trials characteristics.

Study ID	Study Design	Population	Sample size		Mammography duration of screening	Mammography screening Interval (months)	Attendance	Control group intervention	Follow-Up	Main Results
			MG	CG						
Canada Study	RCT	Women aged 40-59, had had no mammography in the previous 12 months, had no history of breast cancer, and were not pregnant.	44925	44910	5	12	88%	Physical and self-examination	25	Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available.
Edinburgh Study	RCT	Woman aged 45–64 years without a previous diagnosis of breast cancer were eligible for entry to the trial	28628	26026	6	24	65%	None	14	Screening for breast cancer lowers breast-cancer mortality. The results for younger women suggest benefit from introduction of screening before 50 years of age.
Gothenburg Study	RCT	Women aged 39 – 59 years	21650	29961	7	18	84%	None	24	The policy of offering mammographic screening substantially reduces

										breast cancer mortality and can do so in women younger than 50 years
Malmo" I & II	RCT	All women under age 50	21242	21240	12	18-24	74%	None	30 & 22	The continued follow-up of the mammographic screening activities in the city of Malmo ¨ lends support to the view that the relative risk reduction with regard to breast cancer mortality is similar in women below and above 50 years of age. The harm benefit analysis indicates that the effect on mortality in premenopausal women may be associated with serious costs in terms of detection of clinically insignificant tumors, false positive findings, and even radiation-induced cancers.
New York	RCT	Women aged 40-	31092	31092	3	12	65%	None	18	The reduction in the

HIP		64 years were selected								decrease in mortality casts doubt on the ability to conclude from the HIP study that initiation of screening under the age of 50 is efficacious
Stockholm	RCT	Women aged 40 through 64 years.	40318	20000	4	24-28	82%	None	25	The breakpoint for benefit in this study seemed to be at 50 years of age when 5-year age groups were analysed, but this tendency is uncertain because of the low statistical power in the analysis of the younger age groups.
Swedish Two-County Study	RCT	Women aged 40–74 years	77080	55985	7	24-32	85%	None	29	Invitation to mammographic screening results in a highly significant decrease in breast cancer–specific mortality. Evaluation of the full impact of screening, in particular estimates of absolute benefit and number needed to screen, requires

										follow-up times exceeding 20 years because the observed number of breast cancer deaths prevented increases with increasing time of follow-up
UK Age trial	RCT	Women aged 39 - 41 years	53884	106956	8	12	81%	None	10	Although the reduction in breast-cancer mortality observed in this trial is not significant, it is consistent with results of other trials of mammography alone in this age-group. Future decisions on screening policy should be informed by further follow-up from this trial and should take account of possible costs and harms as well as benefits.

RCT: Randomized controlled trial; HIP: Health Insurance Plan; MG: Mammography group; CG: control group.

Risk of Bias Assessment: The quality of the included RCTs was from moderate to high quality according to the Cochrane risk of bias assessment tool. Summary of quality assessment domains of included studies is shown in Figure. 2.

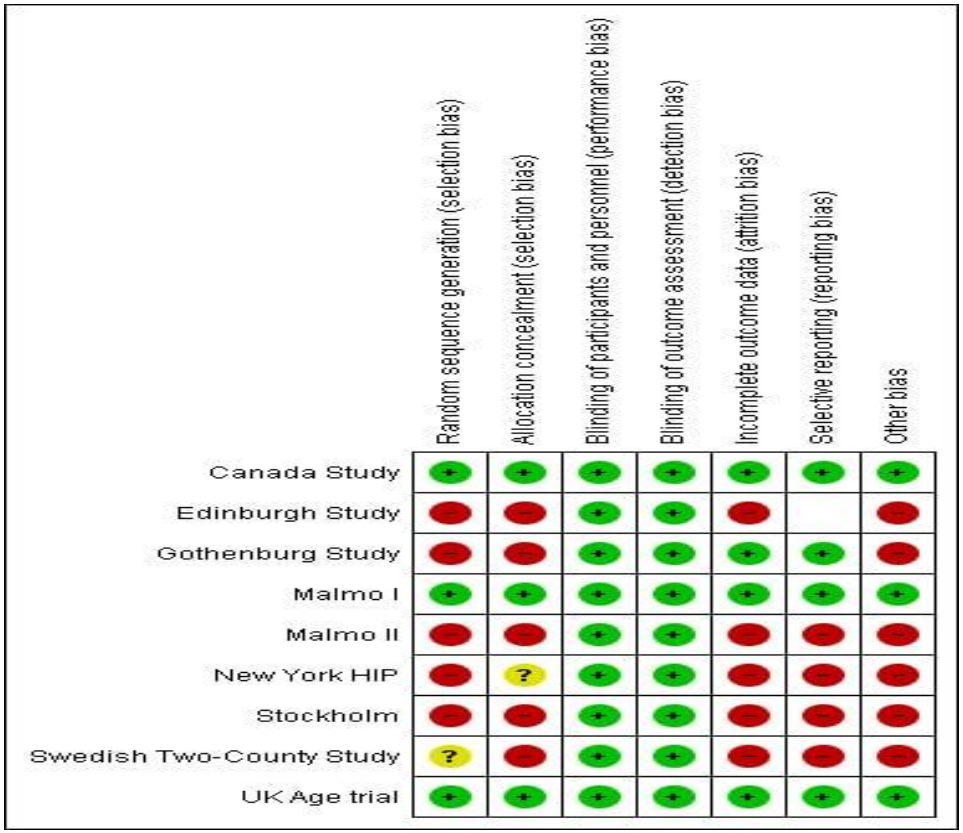

Figure. 2: Summary of quality assessment domains of included studies.

Mammography effect on breast cancer mortality: All included trials reported the breast cancer mortality at the end of follow-up. The overall effect estimates favored mammography group over control group (RR 0.84 (95%) CI [0.75, 0.93]; P =0.001; **Figure.3**). The pooled effect estimate was moderately heterogeneous (P =0.1; I^2 =40%). The relative risk reduction was 16% in breast cancer mortality in women invited for screening.

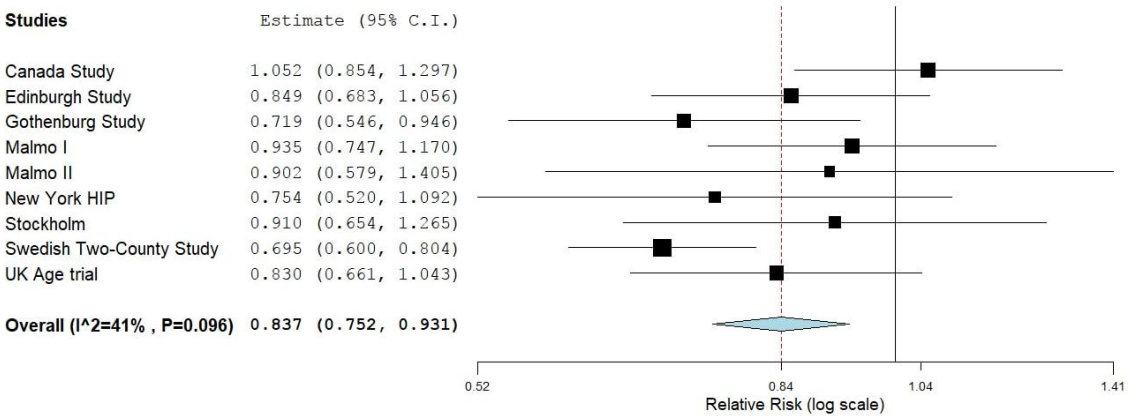

Figure. 3: Mammography effect on breast cancer mortality.

Mammography effect on all cancer mortality: Six included trials reported the all cancer mortality at the end of follow-up. The overall effect estimates did not favor mammography group over control group (RR 1.02 (95%) CI [0.95, 1.10]; P =0.82).

Over diagnosis

We obtained the data from Canada and Malmö studies for the calculation of over diagnosis. The overall percentage of over diagnosis, defined excess cancers as a proportion of cancers diagnosed over long-term follow-up in women invited for screening, was 10.7% (95% CI[9.35, 12.2] Figure.4). The pooled effect estimate was homogenous (P =0.27; I^2 =22%).

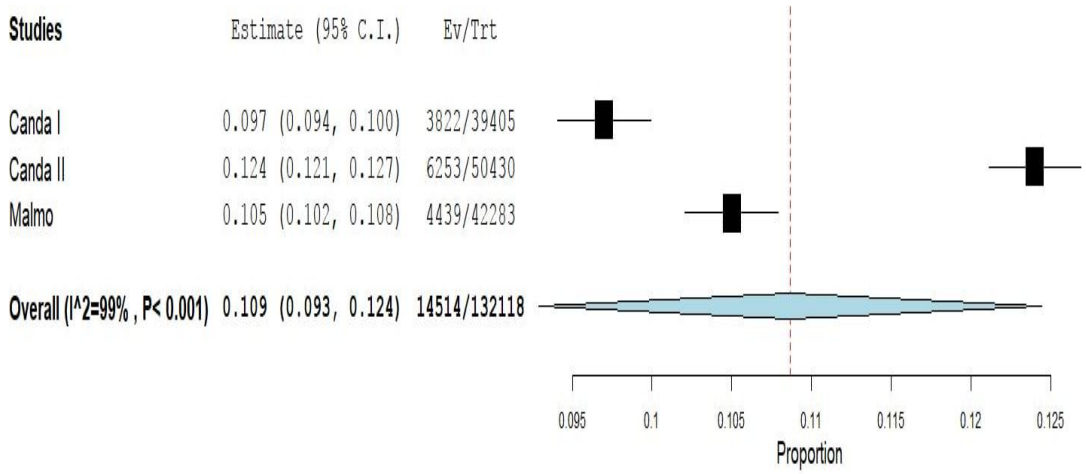

Figure. 4: Calculation of over diagnosis.

DISCUSSION

Screening mammography is widely considered as the most helpful diagnostic tool for early detection of breast cancer, and one of the factors that shaped the marked decreasing in breast cancer mortality in the past three decades.[22,23] Mammography screening every two years is

recommended for women aged between 50 and 74 as well.[10] In the current systematic review and meta-analysis, we included 11 RCTs that addressed the benefits and harms of mass screening mammography. Our pooled effect estimates revealed a statistically significant reduction in breast cancer mortality following screening mammography, with a relative risk decreasing was 16% in mortality of breast cancer among women whose invited for screening. Thus single breast cancer death prevented for about 1539 women screened. Moreover, the overall percentage of over diagnosis was 10%.

The main aim for the introduction of mass screening mammography is to improve the prognosis by earlier intervention; which in return will lead to significant reduction in mortality of breast cancer. Since 1975, there was a reported marked decreasing in mortality of breast cancer (34%); which can be referred to improved treatment protocols, risk factors prevention, and mass screening mammography.[24] In the present review, mortality of breast cancer was selected as the primary outcome. Our results showed that screening mammography significantly decreases the mortality of breast cancer by 16% after a follow-up duration ranged from 14 to 30 years. In concordance with our results, the recent United Kingdom Panel on Breast Cancer Screening reported that screening mammography reduced the mortality of breast cancer by 20% after thirteen years of follow-up.[25] Also, Nystrom and colleagues reported, in their overview of the Swedish randomized controlled mammography trials, a 15% significant relative decreasing in mortality of breast cancer because of an invitation to screening by mammography.[18]

However, there is no clear unanimity in the published literature about the beneficial function of mammography in reducing mortality of breast cancer. The most recent Cochrane review about the effectiveness of screening mammography reported that mammography decrease mortality of breast cancer in the rate of 15%, however, the reduction was not statistically significant.[7] In their overview of the systematic review, Raichand and colleagues concluded that the published reviews showed no consistent conclusions and the evidence cannot be concluded based on them.[26] In the present review, the overall effect estimates showed considerable heterogeneity and the included RCTs did not report similar conclusions (See Figure.1 and Table.1).

Such discrepancies in the published literature can be attributed to a variety of causes. The quality of the included trials within the review may be one of them. Gøtzsche and Jørgensen showed that a significant difference in the reported RR between trials with adequate

randomization and trials without.[7] In the present review, the majority of the included RCTs did not employ adequate methods of randomization. Another possible explanation for the diversity is the different age groups. The age range of the women within the included trials ranged from 39 to 74 years old. The Swedish Two-County study was the only trial that included women above 64 years old[16]; while the UK Age trial included women between 39 and 41 years old only.[17] A previous meta-analysis suggested that mammography is beneficial for women at least 50 years of age.[7] While the 2009 U.S. Preventive Services Task Force showed a lack of evidence that supports the mammography effectiveness in decreasing the mortality of breast cancer among women in their 40s and 70s.[6]

A major concern with mass screening is the diagnostic accuracy of such technique. False positive resultsmay lead to significant, sometimes prolonged, psychological distress.[27] Salz and colleagues performed a meta-analysis of 17 studies (n=20781) that reported the psychological impact of false-positive rates of screening mammography on women. They concluded that the false positive results are significantly associated with psychological distress and anxiety.[28] Previous studies reported a wide range of false positive rates that ranged from 20% to 60%. The UK Age trial reported that over 14.6% of the studied women and 18.1% of women presenting at least one routine screen, had experienced one false-positive screen or more; while the cumulative false-positive proportion over 7 screens was 20.5%.[29] Another study after 10 years of yearly screening, more than 50% of women will receive at least one false-positive recall, and 7% - 9% will receive a false-positive biopsy recommendation.[30]

However, the main disadvantage of screening, according to the independent UK panel, is over diagnosis; over diagnosis is the “detection of cancers that would never have been found were it not for the screening test”.[31,32] The over diagnosis may negatively impact the well-being of the affected women. In the present review, the overall percentage of over diagnosis was 10%; which was similar to the independent UK panel results. However, the Cochrane review reported an over diagnosis of 30%.[7] Moreover, a number of large observational studies reported incidence rates of 40% to 60% in Australia, Finland, Norway, Sweden, UK and USA0.[33,34]

The present systematic review and meta-analysis has a number of strength points. We conducted a comprehensive search of medical databases; and performed the review according to Cochrane collaboration and PRISMA statements guidelines.[35,36] However, we

acknowledge that we have some limitations. The majority of the included trials were of a low quality which introduces biases to the pooled effect estimates. In addition, we could not resolve the detected statistically significant heterogeneity in the pooled effect estimates.

In conclusion, screening mammography has a modest beneficial effect on mortality of breast cancer. But high rates of over diagnosis. The current published literature shows no consensus about harm/benefit balance of mammography, and alarge number of the available clinical trials are of low methodological quality.

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